RESEARCH

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THE following pages give a brief account of research in pharmacology, pathology, immunology and bacteriology carried out by workers at The Wellcome Research Laboratories, England, during the present century.

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THE WELLCOME FOUNDATION LTD.

The Wellcome Foundation is a unique organisation. It is registered as a private limited liability company, but all the shares are vested in five Trustees, whose aim, in the words of Sir Henry Wellcome's will, is—

> " *the advancement of research work bearing upon medicine, surgery, chemistry, physiology, bacteriology, therapeutics, materia medica, pharmacy and allied subjects, and any subject or subjects which have or at any time may develop an importance from the invention and improvement of medicinal agents and methods for the prevention and cure of disorders and the control or extermination of insect and other pests which afflict human beings and plant life in tropical and other regions and elsewhere.*"

They are also empowered to establish or endow research museums and libraries in any part of the world, and to give financial assistance for the collection of information of every kind connected with the history of medicine and allied sciences.

Burroughs Wellcome & Co. is the name under which the original partnership set up in 1880 between S. M. Burroughs and Henry S. Wellcome survives today. On the death of Mr. Burroughs in 1895 it became a one-man undertaking, and in 1924 was merged with the late Sir Henry Wellcome's other interests and assets in The Wellcome Foundation Ltd. Its organisation is world wide for the distribution of products made in the laboratories and works of The Foundation. Henry Wellcome's benefactions and unceasing interest in the prevention and cure of disease received official recognition when he was knighted as " a Generous Supporter of Medical Research," and when he was made a Fellow of the Royal Society under a special statute which allows the election of benefactors of research. Other honours included the honorary degrees of LL.D. and D.Sc., and an honorary F.R.C.S. He died in 1936 at the age of 82.

The Wellcome Foundation's research activities are carried on in a number of Units varying considerably in character and in the nature of their work. Some Units are occupied solely with research or education, as, for example, The Wellcome Historical Medical Museum, The Wellcome Museum of Medical Science and The Wellcome Laboratories of Tropical Medicine. Other Units, such as The Wellcome Research Laboratories, are concerned both with fundamental research and with the preparation of therapeutic agents.

Distribution of products is carried out by Burroughs Wellcome & Co. in England, and by its associated houses in New York, Montreal, Sydney, Cape Town, Bombay, Shanghai, Buenos Aires, Cairo and Dublin. A branch office of the New York house is established in San Francisco.

THE WELLCOME RESEARCH LABORATORIES

The Wellcome Physiological Research Laboratories, as they were called at that time, were founded in London in the year 1894 as a direct result of the publication of Roux's paper on the serum treatment of diphtheria, their object being the production of antitoxic sera. They were the first commercial laboratories in the British Empire to be formed for this purpose.

Less than two years later, the following statement was made in the Wellcome Medical Diary (then known as the A.B.C. Medical Diary) :—" To assist in determining the real clinical value of Anti-Diphtheritic Serum during the period it was under trial, and when diphtheria was unusually prevalent and the demand for the serum a thousand times greater than the then possible rate of production, we supplied it free to physicians, hospitals and infirmaries, when as much as £10 per tube was offered for it, for use abroad. This may, perhaps, be taken as evidence that our efforts in this direction have not been entirely selfish."

Through the years, the work of the Laboratories has continued in the same spirit. Though sera are manufactured there, the Laboratories have always endeavoured to advance the fundamental background of therapeutics.

A view of one of the Chemical Research Laboratories

THE STAFF

In 1898, the Laboratories were moved from Central London to Brockwell Hall, Herne Hill, a 10-acre estate which included stables and buildings suitable not only for the preparation of sera but also for research. At that time no commercial laboratory was permitted to carry out experiments on living animals, but Wellcome, whose aim was the advancement of medical science rather than manufacture only, determined to make his Laboratories a research centre in fact as well as name. Despite considerable opposition from influential quarters, he gained his object at the beginning of the present century and The Wellcome Physiological Research Laboratories were registered as a place where such experiments could be performed—the first commercial research unit of its type in Britain.

The then Director, Dr. Walter Dowson, attracted a number of enthusiastic men to work under him. The calibre of these men may be gauged from the fact that the scientific staff until the outbreak of war in 1914 never numbered more than twelve, yet no less than eight of these subsequently became Fellows of the Royal Society, two being knighted. They were H. H. Dale (Sir Henry Dale, O.M., Nobel Laureate, President of The Royal Society, 1940–45), P. P. Laidlaw (the late Sir Patrick Laidlaw, co-discoverer of the methods of immunisation against dog distemper), G. Barger (late Professor of Chemistry, Edinburgh), J. H. Burn (Professor of Pharmacology, Oxford), A. J. Ewins (Director of Research, May & Baker, Ltd.), A. T. Glenny (who retired in 1947), H. King (Chemist in the M.R.C. Laboratories), and J. Mellanby (late Professor of Physiology, Oxford).

In 1906, Dr. Dale succeeded Dr. Dowson as Director, and remained there until the outbreak of the first world war when he, together with Dr. Barger and Dr. Ewins, joined the research team then being built up by the Medical Research Committee (now the Medical Research Council). At about the same time, Dr. Laidlaw accepted the position of Professor of Pathology at Guy's Hospital. Shortly before this, it had been decided to enlarge the scope of the Laboratories to cover the veterinary field. Until 1912, the veterinary staff was engaged only in the supervision of the horses necessary for the production of sera and vaccines for human use, but in that year the first Veterinary Superintendent, Mr. J. B. Buxton, then lecturer in Veterinary Hygiene, Royal (Dick) Veterinary College, was appointed.

The war provided fresh problems. Dr. R. A. O'Brien, successor to Dr. Dale, was faced with the necessity of increasing the production of serological products. Research had to be restricted but, with the reduced scientific staff, this was inevitable in any case.

With the armistice came the task of re-establishing the research side. Of the original team few remained. Dr. Mellanby was lecturer in physiology at St. Thomas's Hospital, J. H. Burn was studying medicine at Oxford and Dr. King was shortly to leave for the Medical Research Council.

Sir Henry Wellcome, not the least of whose gifts was his ability to recognise young men of promise, appointed Dr. P. Hartley in 1919, Dr. J. W. Trevan in 1920, and Dr. J. H. Gaddum in 1925, all three of whom were later elected Fellows of The Royal Society. Dr. Hartley resigned in 1921 to go to the National Institute for Medical Research, and was knighted in 1944. Dr. Gaddum, who joined the same institute in 1927, is today Professor of Pharmacology at Edinburgh. Dr. Trevan is still with the Laboratories and has been its Director since 1941 when he succeeded Dr. O'Brien.

Expanding research called for larger premises so in 1922, a move was made to the present site, Langley Court, Beckenham, Kent, an estate of rather more than 100 acres. A year later the present director of clinical research, Dr. H. J. Parish, joined the staff.

On the veterinary side, Mr. Buxton relinquished his post on becoming Director, Farm Laboratories, Medical Research Council, in 1922. He was succeeded by Mr. T. Dalling (now Sir Thomas) the present Chief Veterinary Officer of the Ministry of Agriculture and Fisheries and Director of the Ministry's Veterinary Laboratories at Weybridge. Mr. Dalling was followed in 1937 by Dr. R. F. Montgomerie, the present Director of Veterinary

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Research. Dr. Montgomerie was president of the National Veterinary Medical Association of Great Britain and Ireland in the year 1948–9.

Many other men of eminence have worked or still are working at The Wellcome Research Laboratories.

RESEARCH: EARLY YEARS

Some 700 papers have been published from The Wellcome Research Laboratories since 1903. They range over a wide field in pharmacology, pathology, immunology and bacteriology and many have greatly influenced scientific thought.

At the opening of the century, the serum treatment of disease was as prominent in the medical world as is the treatment of allergic states today. It is therefore a matter of no small interest that The Wellcome Research Laboratories have played a major role in investigating both subjects.

The first pharmacologist, Dr. Mellanby, spent several years studying the globulins and other proteins from horse serum and plasma. His description of a method for concentrating diphtheria antitoxin, without denaturing the protein, by treating the serum with alcohol at low temperatures, laid the foundation for the fractionation of plasma into its components, the globulins, fibrinogen and albumin by Professor E. J. Cohn and his colleagues at Harvard.

Work on the constituents of ergot by Dr. Barger, Dr. Dale, Dr. Ewins and Dr. Laidlaw resulted not only in important information concerning the ergot alkaloids but also in discoveries of even greater importance. Dr. Barger had already, before Dr. Dale joined the staff, started to investigate the chemical constituents of the plant. Ergotoxine was discovered through the recognition of its curious reversal of the pressor action of adrenaline. Histamine, an important terminal link in the chain of causation of allergic reactions, was then isolated and its pharmacological effects analysed by Dr. Dale and Dr. Laidlaw. This led to a study of other amines, many, such as ‘ Epinine,’ being unknown till then. The paper by Dr. Barger and

Withdrawal of hyper-immune blood from a horse

Dr. Dale describing this work was published in 1910 and has been of the deepest significance to physiology. It gave science the word "sympathomimetic." Of interest is the fact that the associated laboratories in New York have, in recent years, introduced a new antihistamine which differs in chemical structure from previous compounds of the same nature. This compound, issued by Burroughs Wellcome & Co. under the brand name 'Histantin,' is notable for its prolonged action and relative freedom from side-effects.

The action of ergot in causing strong contraction of the uterus led Dr. Dale to the study of another powerful oxytocic present in extracts of the pituitary posterior lobe. Dr. Dale and Dr. Laidlaw's methods for standardising such extracts are still in general use today. But the possibilities of ergot were not yet exhausted. In 1914, Dr. Ewins described his identification of acetylcholine in a particular ergot extract, and, in the same year, Dr. Dale showed that this compound produced both muscarine- and nicotine-like activities by which it simulated the effects of different groups of efferent nerves. Thus was the first step made towards the modern conception of the chemical transmission of nervous stimuli, a work which led finally to the award of a Nobel prize to Sir Henry Dale and Professor Loewi in 1936. A complete survey of the ergot alkaloids was later to be made by Dr. A. C. White, the present pharmacologist at Beckenham.

Concurrently with these studies, other work had been proceeding. Dr. G. S. Walpole, who first organised the concentration of antitoxin at the Laboratories, had carried out fundamental work on hydrogen-ion concentration, Mr. Buxton had conducted experiments into the prevention of bovine epizootic abortion, and Mr. Glenny was already earning a reputation in the serological field. As early as 1904, he used diphtheria toxoid for the active immunisation of horses. Between 1910 and 1912 he and Dr. H. J. Südmersen described the variation in susceptibility of guinea pigs to diphtheria toxin, their immunity to it and the effect on the offspring. A year later he described a modification of diphtheria antitoxin.

One of the cold stores

Part of the serum concentration plant

SEROLOGICAL RESEARCH AFTER 1918

From the end of the war in 1918, Mr. Glenny's most productive work is seen. In 1921, with Dr. Südmersen, he described "primary" and "secondary" stimuli in diphtheria prophylaxis, thereby outlining the principles which govern all accepted methods of immunisation with toxins and their derivatives today. Two years later, he and Miss B. E. Hopkins first suggested diphtheria toxoid as an immunising agent for man. Then, in 1926, came the important announcement that he and his collaborators, Dr. C. C. Pope, Miss H. Waddington and Miss U. Wallace had found the antigenic value of toxoid to be enhanced by the addition of alum. By 1931, with Miss Mollie Barr, he was able to recommend the use of this alum precipitated toxoid (A.P.T.) as an antigen, the efficiency of which he, with Dr. G. A. H. Buttle and Miss M. F. Stevens, showed to be due to slow absorption and excretion.

Dialysis : a stage in the purification of sera

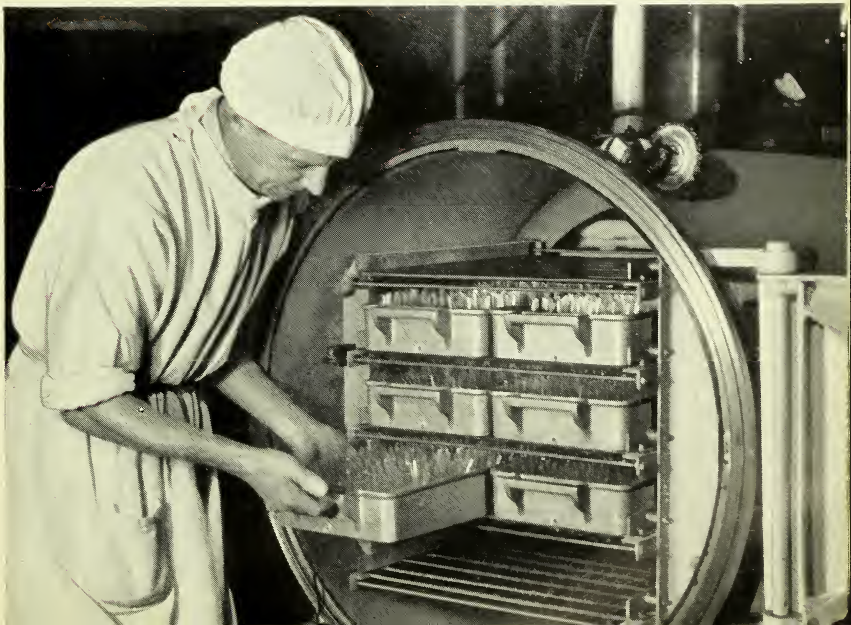
Four years previously, he and Dr. Pope had prepared toxoid-antitoxin floccules (T.A.F.) for human use. Thus the two prophylactics which have made possible the success of the present Diphtheria Immunisation scheme in Great Britain both came from The Wellcome Research Laboratories. Nor were these the only contributions of the Laboratories to the prevention and treatment of this disease. Dr. O'Brien, a pioneer advocate of active immunisation against diphtheria, was the first person in Great Britain to carry out Schick testing, his observations being greatly extended later by Dr. Parish and Dr. C. C. Okell.

As the Laboratories had been engaged in the preparation of diphtheria antitoxin, it is not surprising that the efficient methods of purification should have been evolved there. During 1920 and 1921, Dr. Hartley developed a medium for the production of the toxin which has found world-wide use. He was also a pioneer in low temperature drying of sera and other protein solutions. In 1938–39, Dr. Pope introduced a new method of purifying the antitoxin by enzyme refinement and heat treatment. This process, which not only produces high unitage in small volume but also reduces non-specific protein to a minimum, thereby lessening the risk of serum reactions, is today used for the refinement of all antitoxic sera for human use prepared at Beckenham.

Large volumes of tetanus antitoxin were prepared by the Laboratories during the first world war. Shortly afterwards, Buxton and Glenny described their method of producing this antitoxin by the injection of horses with toxin-antitoxin mixtures followed by toxin. With the introduction, during the 1930's, of tetanus toxoid for active immunisation, Mr. Glenny studied this subject, and, in 1938 with Miss Stevens, described methods for testing the immunising power of tetanus prophylactics and for the antitoxic titration of small quantities of human sera.

The assay of scarlatina antitoxin produced three important papers, that of Dr. Parish and Dr. Okell in 1927 describing an intravenous method in rabbits ; that of Dr. Buttle and Miss A. S. R. Lowdon in 1935 on a modified titration of toxin and antitoxin in the skin of rabbits ; and that of Mr. H. Proom in 1941 on an improved flocculation test. The production of staphylococcus toxoid and

Freeze-drying, ampoules being removed from desiccator



Inoculation of culture media with diphtheria bacilli for the preparation of toxoid

antitoxin was made easier with the introduction by Dr. Parish and Miss W. H. M. Clark, in 1932, of a modified method of extracting the toxin from agar on which the organisms have grown. Three years later, Mr. Glenny and Miss Stevens differentiated between the α and β toxins produced by staphylococci.

Not the least important of the many papers published in the inter-war period are those dealing with the *Cl. welchii* group, a short description of which is given in the section of the booklet, " Veterinary Research after 1922 " (*page* 14).

During the second world war, immunological research activities were partly curtailed. Now they are again being pursued as actively as possible ; already the production of diphtheria toxin by deep culture, and a new method of refining antibacterial sera by precipitation with ammonium sulphate in the presence of tricresol have been described.

PHARMACOLOGY AFTER 1918

The workers at The Wellcome Research Laboratories continued to make important contributions to pharmacology. Dr. Trevan's first paper, written in collaboration with Mr. E. M. Boock, " Action of Anæsthetics on Respiratory Centre," appeared in the Journal of Physiology in 1921. It was followed by others covering a wide field. In physiology his researches have included studies of renal secretion, of the nervous control of respiration and of changes in traumatic shock. In pharmacology he has worked on the toxins produced by anærobic bacteria, on snake venoms, and on the mode of action of local anæsthetics and analeptics. In 1927, appeared his most important single piece of work "The Error of Determination of Toxicity." Concerned with the application of statistical methods to the biological assay of drugs, it has had a world-wide influence on the design of methods of bio-assay. His invention of a micrometer syringe (the ' Agla '), in 1925, provided an instrument of high accuracy for the titration of fluids in microbiology.

In 1928, Dr. Buttle and Dr. Trevan described the action of *Vibrion septique* and *B. welchii* on isolated organs. Biological assay, as evidenced by papers on digitalis and crystalline insulin, formed no small part of the pharmacological work between the wars.

Section of one of the small-animal rooms

In the period immediately before the second war, Dr. Buttle and his co-workers carried out a wide survey of chemotherapeutic agents, particularly sulphone derivatives and sulphonamides. Of the many compounds then synthesised, two—Sulphaguanidine and ‘ Sulphetrone ’—have proved most useful. ‘ Sulphetrone ’ is today recognised as the drug of choice in the treatment of lepromatous leprosy.

Research continued through the war, though on a restricted scale. The antibiotics, penicillin and streptomycin, were studied and a search was made for other substances of a like nature. Four out of five of the known polymyxins, a group of antibiotics derived from *B. polymyxa*, were discovered at Beckenham and a great deal of important work was done concerning their structure. These antibiotics cover part of the bacterial spectrum not filled by penicillin or streptomycin, but, because of varying degrees of toxicity, they have not fulfilled the high hopes which were at first formed of them.

With the end of hostilities, research projects were increased. Opportunity being given for a study of war-time research in Germany, Dr. A. C. White turned his attention to the investigation of new remedies. As a result, ‘ Physeptone,’ an analgesic more potent than morphine but less liable to cause addiction or side-effects, and ‘ Neo-Epinine,’ an adrenaline analogue with relative freedom from side-effects for the treatment of asthma, have been introduced to the medical profession by Burroughs Wellcome & Co.

VETERINARY RESEARCH AFTER 1922

With the removal of The Wellcome Research Laboratories to Beckenham in 1922, veterinary research was greatly expanded. Mr. Dalling brought with him a number of problems on which he had been working in Scotland, in particular lamb dysentery and braxy in sheep. He, Glenny, Miss Barr, Miss M. Llewellyn-Jones and Miss H. Ross classified the organisms of the *Welchii* group and demonstrated their production of multiple toxins. During this investigation, Mr. Dalling, Dr. J. H. Mason (now head of the Serum Department of the South African Institute for

The paddock at Frant

Medical Research) and Dr. W. S. Gordon (today, Director of the Agricultural Research Council Station at Compton) did their classical work on the transference of maternal immunity. Demonstrating that the lamb is born free from infection but quite unprotected, they proved that protection can be derived from antibodies present in the colostrum of the ewe. As a result they were able to describe the two methods of immunisation in use today against lamb dysentery—vaccination of the ewe or injection of the young lamb with serum. This work led naturally to the investigation of associated diseases, particularly pulpy kidney disease of lambs and sheep.

In 1928, Dr. Laidlaw and Major Dunkin, working for the Medical Research Council and supported by the Field Distemper Fund, completed their studies on dog distemper. The Wellcome Research Laboratories were then asked to prepare distemper prophylactics on a large scale. This involved extensive researches which are being continued to the present day.

In 1925, " yellows " in dogs was shown by Mr. Dalling, Dr. Okell and Mr. L. P. Pugh to be due to *Leptospira icterohæmorrhagiæ*, the causative organism of Weil's disease in man. Studies of major diseases of the cat resulted in " cat distemper " being distinguished from " feline infectious enteritis," for which an effective vaccine was prepared.

As a result of studies on poultry, the first large-scale testing for carriers of bacillary white diarrhœa (B.W.D.) in this country was established at Beckenham in 1929. Mr. Dalling and his collaborators were among the first to demonstrate the occurrence of *salmonella* infection in duck eggs and to develop an agglutination test for the detection of carrier ducks.

Dr. R. F. Montgomerie, who succeeded Mr. Dalling in 1937, had been scarcely two years in the post when he was faced with the problems of war-time conditions. Research was therefore restricted in the main to improvement of serological products. With the end of hostilities, however, opportunity became available to re-open investigations into canine disease, the most notable study being that relating to encephalitis in this species by Mr. A. B. MacIntyre and Dr. D. J. Trevan, who demonstrated and described the so-called " Hard Pad " disease.

Since 1943, veterinary research has also been carried out at The Wellcome Veterinary Research Station, Frant, which is under the direction of Dr. Montgomerie with Mr. S. L. Hignett as Resident Veterinary Surgeon. The principal subjects of research there are those associated with the problem of reproduction in horses, cattle and dogs. Important contributions have also been made to the control and treatment of bovine mastitis.

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